Scientific Abstract or Project Summary for NIH Reviewers

Peripheral vascular disease (PVD) is a significant health problem in the United States with an age-adjusted prevalence of 12%. The clinical consequences of this problem are staggering, with over a million people being diagnosed every year with PVD. The most common cause of PVD is occlusive atherosclerosis of the lower extremities. The manifestations of PVD include intermittent claudication (pain on walking), rest pain and loss of tissue integrity in the distal limb (gangrene). A variety of treatments are available presently for this condition, including medical therapy, percutaneous intervention and surgical bypass techniques. In spite of the availability of these modalities there seems to be a need for the development of more effective techniques. One such modality is therapeutic angiogenesis or the creation of new networks of blood vessels that provide a system of collateral circulation, that then provide a bypass mechanism. The process of angiogenesis is complex and likely involves several mediators acting in concert to produce new vessels in an orderly fashion. One of the most important mediators of the angiogenic process is Vascular Endothelial Growth Factor (VEGF). VEGF is a single gene product that is secreted as four different isoforms secondary to post-transcriptional splicing.

A number of pre-clinical studies have demonstrated the efficacy of VEGF protein in inducing angiogenesis. Further a few studies have examined direct gene transfer of "naked"(plasmid) DNA for VEGF165 with promising early results.

The purpose of this protocol is to evaluate the safety and efficacy of therapeutic angiogenesis in-patients with PVD using an adenoviral delivery system AdVEGF121.10, carrying the gene for VEGF121. Adenoviral vectors are effective at transferring genes to skeletal muscles, with high levels of gene expression for at least a week. Accordingly, we propose to intramuscularly administer AdVEGF121.10 in a double blind placebo controlled fashion to patients with severe PVD. The objective of the study will be to determine if administration of AdVEGF121.10 results in growth of new blood vessels and improvement in function in the region of ischemia.